CLL-FRAIL: SUMMARY OF RESULTS

CLL-Frail Protocol of the German CLL-Study Group (GCLLSG)

A PROSPECTIVE, MULTICENTRE PHASE II TRIAL OF ACALABRUTINIB IN VERY OLD (≥ 80Y) AND/OR FRAIL PATIENTS WITH CLL

Version	v1.0	**Effective date**	30.12.2025
EU-CT Number:	2023-507002-14-00	**Registry-Number, Sponsor's Number**	NCT04883749, Uni-Koeln-4315

Contents

Abbreviations and definitions

AE	Adverse Event
CIRS	Cumulative Illness Rating Scale
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRi	Complete response with incomplete marrow recovery
CRF	Case Report Form
CT	Computed Tomography
DMC	Data Monitoring Committee
EFS	Event-free survival
EORTC-QLC30	European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30
FAS	Full Analysis Set
GCLLSG	German CLL Study Group
IC	Informed Consent
IND	Investigational New Drug
IQR	Interquartile range
IRA	Initial response assessment
ITT	Intention to treat
IV	Intravenous
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Minimal residual disease
nPR	Nodular partial response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PLL	Prolymphocytic leukemia
PR	Partial response
PR-L	Partial response with lymphocytosis
QoL	Quality of life
SAE	Serious adverse event
SD	Stable disease
SMT	Study Management Team
SP	Safety population
TTNT	Time to new CLL treatment
WHO	World Health Organization

A. CLINICAL TRIAL INFORMATION

1. Clinical trial identification

A prospective, multicenter phase-II trial of acalabrutinib in very old (≥80y) and/or frail patients with CLL
EudraCT number: 2020-002142-17
Trial protocol: DE, AT
Global end of trial date: 08.05.2025

2. Identifiers

Sponsor protocol code: CLL-Frail
NCT Number: NCT04883749
EU CT Number: 2023-507002-14-00
Sponsor Number: Uni-Koeln-4315

3. Sponsor details

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4. Pediatric regulatory details

Not applicable.

5. Result analysis stage

Analysis stage:	Final
Date of final analysis:	08.05.2025
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date:	08.05.2025
Was the trial ended prematurely?	No

6. General information about the clinical trial

Trial design: The CLL-Frail trial is a prospective, multicenter phase-II trial.

Primary objective: The primary objective of the trial is to show the efficacy of acalabrutinib in a cohort of CLL-patients aged 80 or older and/or with a score of > 2 assessed in the FRAIL scale. The efficacy is assessed by measuring the overall response rate (ORR) at initial response assessment after 6 cycles of treatment. The primary endpoint is measured in patients receiving at least one dose of treatment greater than 0 mg in the fourth cycle of treatment (modified full analysis set [modified FAS]).

Scientific background and rationale: Elderly patients over 80 years remain an underrepresented age group in clinical trials for CLL, even though they account for a relevant number of patients. The proportion of elderly patients is expected to grow in the near future, which leads to the need of a better understanding on how to treat this age group. Since age is not the only factor accounting for fitness, frailty has emerged as a considerable factor with a measurable impact on overall survival (OS).
Since several targeted agents such as Venetoclax or BTK inhibitors have become available, the treatment landscape of CLL has face profound changes. Venetoclax-based therapies have been established as the standard-of-care for a large proportion of CLL patients. However, tumor lysis syndrome is a common side effect especially in patients with impaired renal function, which is common in elderly patients. Even though BTK inhibitors are generally considered safe and well tolerated, there is a considerable risk of cardiac effects. This risk is reduced in second generation BTK inhibitors, such as acalabrutinib, because of a higher target selectivity, resulting in less off-target effects.
The CLL-Frail trial is the first trial addressing an elderly/frail population only.

Protection of trial subjects: Safety measures to prevent or to manage known risks associated with CLL, such as infections or cytopenia or known adverse reactions related to the study drug, have been included in the protocol. Chapter 8 of the protocol includes sections how to prevent and manage known side effects, including detailed instruction about premedication, modifications and treatment discontinuation. The protocol includes sections with prohibited medication during the study.

To account for age and frailty of this specific patient cohort an interim safety analysis was performed in the CLL FRAIL trial. The interim safety analysis was triggered once 30 patients have had the opportunity to reach cycle 7 day 1 after initiation of therapy. The interim safety analysis evaluated AEs/AEPI/AESIs including but not limited to falls, fractures, and cognitive impairment/dementia.

Actual start of recruitment:	20.05.2021
Long term follow-up planned:	No
Independent data monitoring committee (IDMC) involvement?	No

Study assumptions and sample size calculation: The primary endpoint ORR at initial response assessment after 6 cycles of treatment was used to determine the sample size of the study. The following study assumptions were considered for patients in the modified FAS:

- The investigated regimen is assessed to be not effective if the ORR is less than 65% with corresponding null hypothesis H_0: ORR ≤ 0.65 and alternative hypothesis H_1: ORR > 0.65.
- The investigated regimen is considered potentially useful and worthy of further research if the null hypothesis in favor of the alternative hypothesis can be rejected.
- It is assumed to improve the ORR to at least 85% with the investigated regimen.

A one-sided one-sample binomial-test with an overall significance level of 2.5% provides the sample size N = 49 for patients with at least one dose of treatment greater than 0 mg in the fourth cycle of treatment, such that statistical significance is achieved with a power of 90% at the assumed ORR of 85%. Patients discontinuing study therapy before receiving treatment with dose greater than 0 mg in the fourth cycle of treatment did not count for the target sample size of 49 and were replaced.
Efficacy analyses: The primary endpoint analysis was performed based on the modified FAS. It was conducted with a data cut-off date of 15th of January 2024 after all enrolled patients, who have not discontinued prematurely, have achieved the landmark of initial response assessment. The ORR was

compared with the pre-specified benchmark of P0 = 65% using a one-sided one-sample binomial test. The corresponding 95% Clopper Pearson confidence interval of the ORR was determined.
Analyses of secondary efficacy endpoints were not tested formally and there was no control of type I error of any secondary endpoint. Every secondary endpoint was descriptively analyzed and reported. Analyses were based on the modified FAS. Secondary rate-based efficacy endpoints were assessed showing frequencies and corresponding percentages. Analyses of secondary time-to-event efficacy endpoints were performed using Kaplan-Meier methods.

Safety analyses: Adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. AEs were reported by MedDRA system organ class (SOC), and preferred term (PT). The severity of the AEs was graded according to the recent updated NCI CTCAE version 5. First, all cases of AEs were reported in a case analysis including the number of events classified as being serious and related to study drugs (according to the investigator). Specifications of AEs leading to death or treatment discontinuation were also summarized. Second, AEs were reported in a by-patient analysis. This means, that an event will be counted once only (with worst NCI CTCAE) if a subject has the same event more than once. Regarding the severity frequency tables were based on all AEs classified as maximum NCI CTCAE Grade 1-2, maximum NCI CTCAE Grade 3, maximum NCI CTCAE Grade 4, maximum NCI CTCAE Grade 5, maximum Grade 1-5 as well as AEs classified as maximum NCI CTCAE Grade 3-5.

Feasibility analyses: Descriptive statistics for continuous variables including median, interquartile range, mean, minimum, maximum, and standard deviation were used. Categorical variables were reported with counts and relative frequencies. Feasibility parameters were reported with respect to the safety population.

7. Population of subjects

Total number of subjects:

Study populations	ITT	SP	Modified FAS
All patients	53	52	46
Enrolled in Germany	37	37	33
Enrolled in Austria	16	15	13

B. SUBJECT DISPOSITION

1. Recruitment

Between June 01, 2021 and July 06, 2023, a total of 55 patients were screened for eligibility and 53 eligible patients were included in the study (intention to treat [ITT] population). Both screening failure were due to not fulfilling inclusion/exclusion criteria.
Randomisation and blinding are not applicable for this trial.

Investigational medicinal produce:	Acalabrutinib
Investigational medicinal produce code:	ACP-196
Pharmaceutical form and route of administration:	Capsules and film-coated tablets, oral intake

2. Pre-assignment Period

A total of 53 patients were included in the study (ITT population). 52 patients started study medication (safety population [SP]); one patient withdrew consent and never received any study medication. The SP was used for evaluating the safety and feasibility endpoints.
Of the 52 patients, 46 patients received at least one dose of acalabrutinib greater than 0mg in the fourth cycle of treatment and were included in the modified FAS. The modified FAS was used for analysis of all study endpoints except safety and feasibility.

3. Post Assignment Periods

Both capsules and film coated tablets of acalabrutinib were used in this study. Patients were instructed to take one 100 mg acalabrutinib capsule/film coated tablet twice daily, every 12 hours. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Acalabrutinib 100 mg was administered daily twice up to active progressive disease with treatment indication according to iwCLL criteria or unacceptable toxicity. Patients were treated for 24 cycles after which a final restaging was performed. Treatment with acalabrutinib could be continued outside the trial at the treating physician's discretion.

Of the 53 enrolled patients, 29 patients had an ongoing treatment until the regular end of study and 23 discontinued the treatment prematurely. Reason for premature treatment discontinuation was refusal to cooperate in 4 patients, AE in 11 patients, 3 patients had an AE and died, one patient had an AE and refused to cooperate, one patient had an AE and withdrew consent, one patient had an AE and went to hospice stay, and 2 patients died.

C. BASELINE CHARACTERISTICS

Baseline characteristics will be reported for the modified FAS and the ITT population.

1. Baseline Characteristics: Age

Age

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Age (years)	**53**		**46**	
Mean	80.47		80.30	
Standard deviation	5.66		5.51	
Median	81		81	
IQR	78 – 84		78 – 84	
Range	54 – 91		54 – 88	
Age (years), N (%)	**53**		**46**	
< 65	1	(1.9)	1	(2.2)
≥ 65	52	(98.1)	45	(97.8)
Age (years), N (%)	**53**		**46**	
< 75	4	(7.5)	3	(6.5)
≥ 75 and < 80	13	(24.5)	12	(26.1)
≥ 80 and < 85	25	(47.2)	22	(47.8)
≥ 85	11	(20.8)	9	(19.6)

2. Baseline Characteristics: Gender

Gender

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Gender, N (%)	**53**		**46**	
Female	16	(30.2)	13	(28.3)
Male	37	(69.8)	33	(71.7)

3. Baseline Characteristics: Study Specific Characteristic

Previous treatment

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Previous treatment, N (%)	**53**		**46**	
Treatment naïve	36	(67.9)	33	(71.7)
Relapsed/refractory	17	(32.1)	13	(28.3)

Binet stage

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Binet stage, N (%)	**53**		**46**	
A	18	(34.0)	16	(34.8)
B	13	(24.5)	10	(21.7)
C	22	(41.5)	20	(43.5)

IGHV mutation status

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
IGHV mutation status, N (%)	**53**		**46**	
Unmutated	32	(60.4)	28	(60.9)
Mutated	21	(39.6)	18	(39.1)

CLL-IPI risk group

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
CLL-IPI risk group, N (%)	**53**		**46**	
Low	1	(1.9)	1	(2.2)
Intermediate	4	(7.5)	3	(6.5)
High	38	(71.7)	34	(73.9)
Very high	10	(18.9)	8	(17.4)

TP53 mutation

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
***TP53* mutation status, N (%)**	**53**		**46**	
Unmutated	46	(86.8)	41	(89.1)
Mutated	7	(13.2)	5	(10.9)

Deletion 17p

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Deletion 17p, N (%)	**53**		**46**	
No	44	(83.0)	38	(82.6)
Yes	9	(17.0)	8	(17.4)

Complex karyotype

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Complex karyotype, N (%)	**53**		**46**	
Non-complex (< 3 aberrations)	45	(84.9)	39	(84.8)
Complex	8	(15.1)	7	(15.2)

Total CIRS score

Patient characteristics	ITT	Modified FAS
All patients	**53**	**46**
Total CIRS score	**53**	**46**
Mean	8.53	8.24
Standard deviation	3.66	3.60
Median	9	8
IQR	5 – 11	5 – 11
Range	2 – 18	2 – 18

Frail scale score

Patient characteristics	ITT		Modified FAS	
All patients	**53**		**46**	
Frail scale score	**53**		**46**	
Mean	2.11		2.09	
Standard deviation	1.54		1.52	
Median	2		2	
IQR	1 – 3		0 – 3	
Range	0 – 5		0 – 4	
Frail scale score, categorical, N (%)	**53**		**46**	
No frail (= 0)	13	(24.5)	12	(26.1)
Pre-frail	15	(28.3)	12	(26.1)
Frail (≥ 3)	25	(47.2)	22	(47.8)

D. ENDPOINTS

1. Endpoint definitions

Primary endpoint: The primary endpoint of the study is the overall response rate (ORR) at initial response assessment (cycle 7, day 1 = approx. 6 months after initiation of therapy). [For patients with at least one dose of acalabrutinib in the fourth cycle and who discontinue prematurely before reaching cycle 7, day 1, the initial response assessment was rescheduled to the time point of treatment discontinuation. For patients who discontinue prematurely before reaching cycle 4, day 1, the initial response assessment was cancelled.]

ORR at initial response assessment is defined as the proportion of patients achieving a CR, CRi or PR (including PR-L) as response (according to the iwCLL 2018 guidelines) at initial response assessment. Patients without documented response at the initial response assessment and patients for whom the initial response assessment was not performed are kept and labelled as 'non-responder' in the analysis.

Secondary endpoints:

1. **ORR at final restaging** (cycle 25, day 1 = approx. 24 months after initiation of therapy).
2. **Overall survival (OS)** was measured from the date of registration to the date of death due to any cause. Patients who have not yet died at the time of analysis were censored at the time of last observation they were assessed to be alive.
3. **Progression-free survival (PFS)** was measured from the date of registration to the date of first occurrence of disease progression or relapse (determined according to the standard iwCLL 2018 guidelines) or death from any cause, whichever occurs first. These were counted as events for PFS. Start of a subsequent anti-leukemic treatment after the study treatment was not counted as an event nor as a reason for censoring. Patients for whom no documented event for PFS is available at the time of analysis were censored at the time point of last observation they were assessed to be event-free.
4. **Event-free survival (EFS)** was measured from the date of registration to the first occurrence of progression or relapse (determined using standard iwCLL guidelines from 201814), death from any cause, or initiation of a subsequent anti-leukemic treatment, whichever occurs first. These were counted as events for EFS. Patients for whom no documented event for EFS is available at the time of analysis were censored at the time of last observation they were assessed to be event-free.
5. **Duration of response** was calculated for all patients with CR, CRi, PR, or PR-L as response at cycle 7 day 1 (initial response assessment) according to the definition of the primary endpoint. It was measured from the date of first documented response (i.e. CR, CRi, PR, or PR-L) to the first occurrence of progression or relapse (determined using standard iwCLL guidelines from 2018) or death by any cause, whichever occurs first. These were counted as events for duration of response. Patients for whom no documented event for duration of response is available at the time of analysis were censored at the time of last observation they were assessed to be event-free.
6. **Time to next CLL treatment (TTNT)** was measured from date of registration to the date of initiation of subsequent anti-leukemic treatment. These were counted as events for TTNT. Alive patients for whom no subsequent anti-leukemic treatment is documented were censored at the time of last observation they were assessed to be event-free. Deceased patients were censored at the date of death.
7. **Safety parameters**: Type, frequency, and severity of adverse events (AEs), adverse events of special interest (AESI), and adverse events of particular interest (AEPI).
8. **Feasibility parameters**:
    - Modification of treatment and reasons.
    - Treatment discontinuation: early discontinuation of treatment and reasons.
    - Treatment exposure: total cumulative dose, dose intensity, time on treatment (any dose), time on treatment (full dose), days with 0 dose.

2. Primary endpoint – ORR at initial response asessment

Primary efficacy analysis[1]	Modified FAS	
All patients	**46**	
Response (initial response assessment), N (%)	**46**	
SD	1	(2.2)
PD	0	(0.0)
Missing	*2*	*(4.3)*
CR	0	(0.0)
PR	43	(93.5)
ORR, N (%)	**46**	
Non-responders	3	(6.5)
Responders	43	(93.5)
ORR	**46**	
Value	0.935	
95% CI (Clopper Pearson)	0.821 – 0.986	
p-value (one-sided)	< **0.001**	

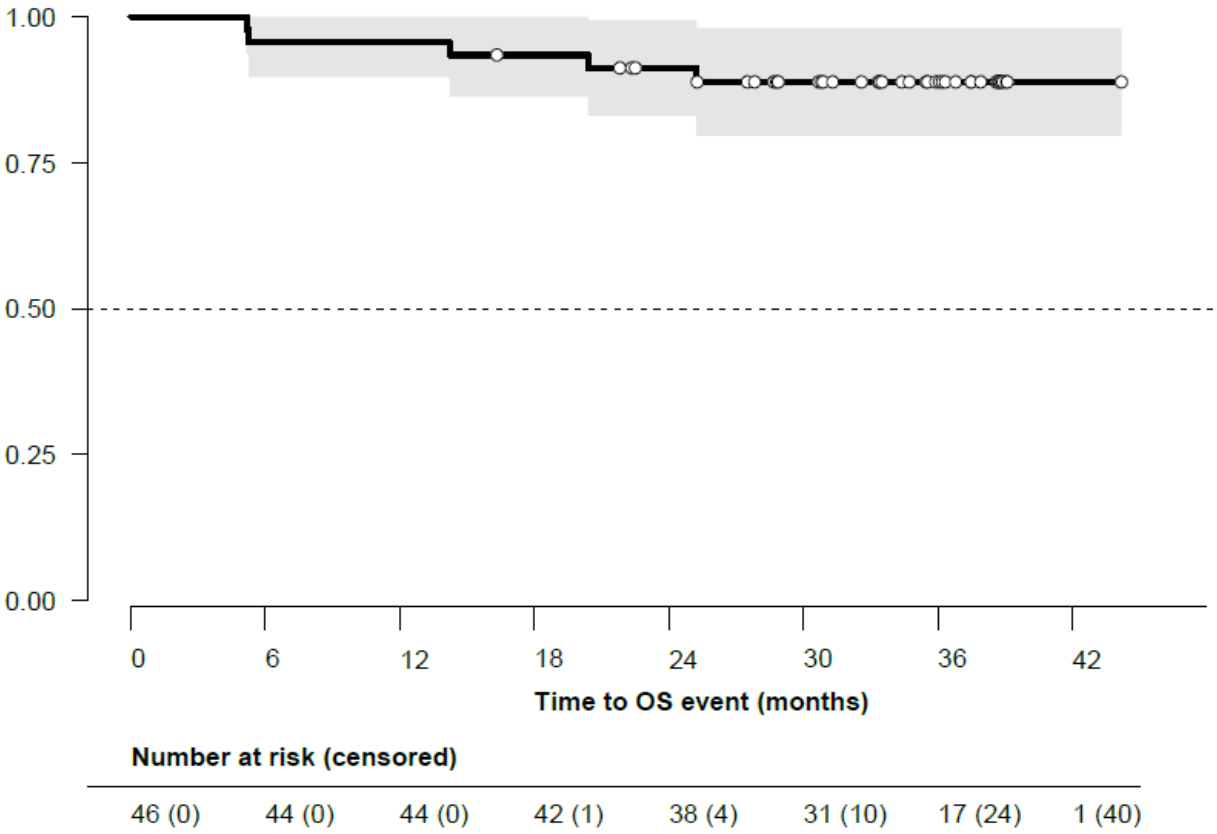
3. Secondary endpoint – ORR at final restaging

Response at final restaging	Modified FAS	
All patients	**46**	
Response (at final restaging), N (%)	**46**	
SD	0	(0.0)
PD	0	(0.0)
Missing	*9*	*(19.6)*
CR	0	(0.0)
PR	37	(80.4)
ORR, N (%)	**46**	
Non-responders	9	(19.6)
Responders	37	(80.4)

[1] The ORR of the study treatment at initial response assessment is compared to the benchmark of 65% using a one-sided one-sample binomial test (with respect to patients constituting the modified FAS).

4. Secondary endpoint – Overall survival (OS)

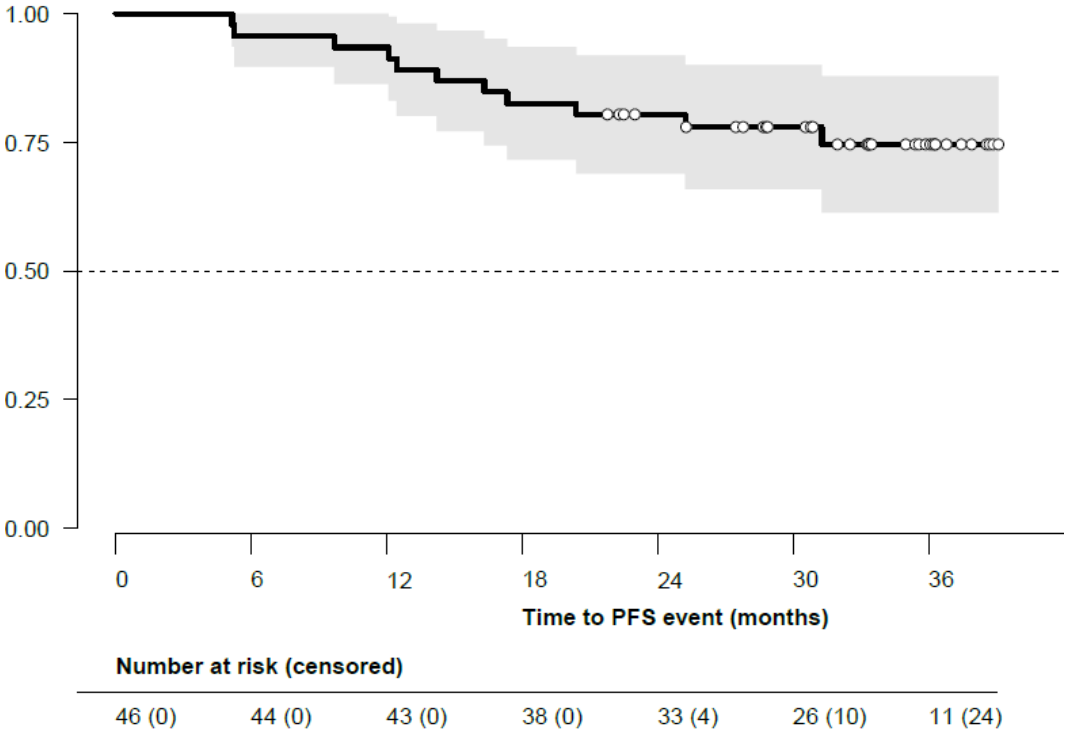
OS	Modified FAS
All patients, N	**46**
Descriptives	
Events, N (%)	5 (10.9)
Median, months [95% confidence interval]	NR
Survival, % [95% confidence interval]	
month 6	95.7 [89.8, 100.0]
month 12	95.7 [89.8, 100.0]
month 18	93.5 [86.3, 100.0]
month 24	91.3 [83.1, 99.4]
month 30	88.9 [79.6, 98.1]
month 36	88.9 [79.6, 98.1]



Cause of death	ITT	Modified FAS
All patients, N	**53**	**46**
Number of deaths, N	**7**	**5**
Concomitant disease, N		
Yes	3	2
Infection (only)**, N**		
Yes	3	2
CLL treatment related and infection, N		
Yes	1	1
Reported cause of death, N		
Covid pneumonia	1	1
COVID19 infection	1	1
Inferior wall myocardial infarction	1	1
Pneumonia with resulting cardiac arrest	1	1
Suspicion of cardiac event	1	1
Pneumonie	1	0
CLL, Parkinson's disease, Lewy dementia	1	0

5. Secondary endpoint – Progression free survival (PFS)

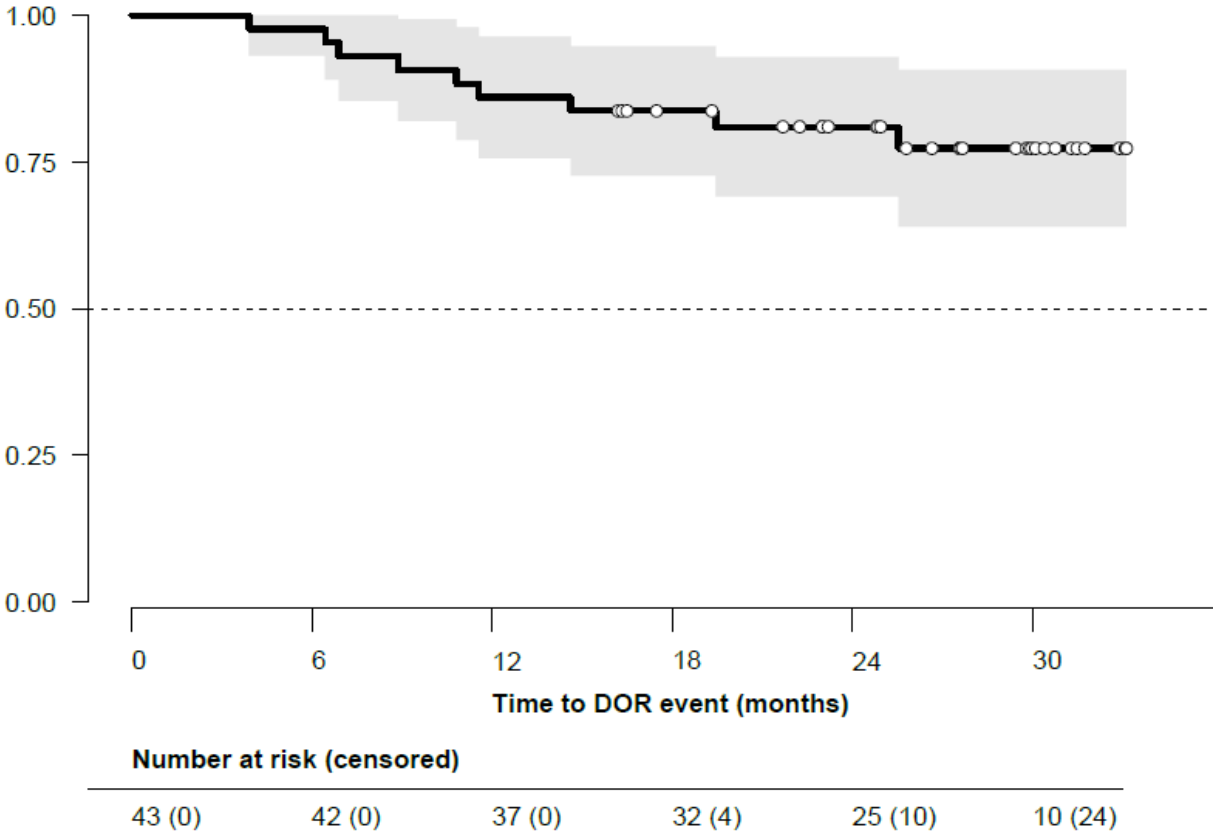
PFS[2]	Modified FAS
All patients, N	**46**
Descriptives	
Events[3], N (%)	11 (23.9)
Median, months [95% confidence interval]	NR
Survival, % [95% confidence interval]	
month 6	95.7 [89.8, 100.0]
month 12	93.5 [86.3, 100.0]
month 18	82.6 [71.7, 93.6]
month 24	80.4 [69.0, 91.9]
month 30	78.0 [65.9, 90.1]
month 36	74.6 [61.4, 87.9]



[2] All patients receiving a new CLL new treatment did so after a disease progression, so that the event-free survival (EFS) coincides with the PFS reported.
[3] Of the 11 PFS events, 5 patients died and 6 had a disease progression.

6. Secondary endpoint – Duration of response (DOR)

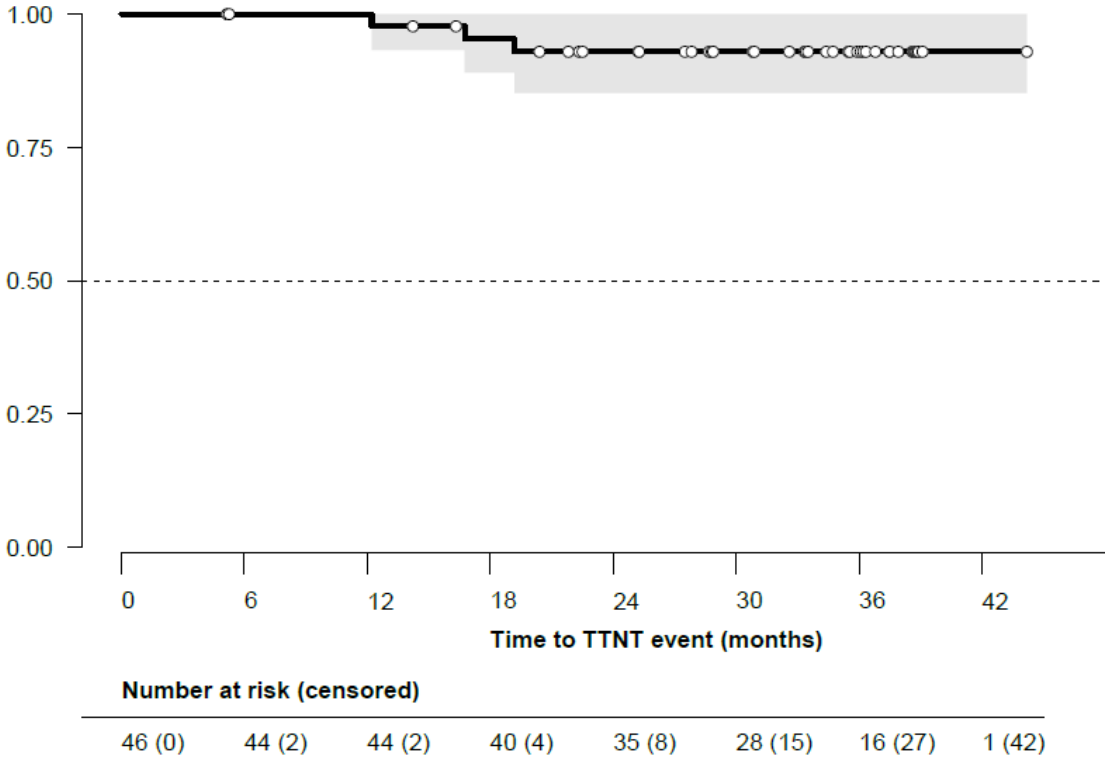
DOR	Modified FAS
All patients, N	46
Number of responders at initial assessment, N	**43**
Descriptives	
Events, N (%)	9 (20.9)
Median, months [95% confidence interval]	NR
Survival, % [95% confidence interval]	
month 6	97.7 [93.2, 100.0]
month 12	86.0 [75.7, 96.4]
month 18	83.7 [72.7, 94.8]
month 24	81.0 [69.1, 92.9]
month 30	77.3 [64.0, 90.7]



7. Secondary endpoint – Time to next CLL treatment (TTNT)

Next treatment	Modified FAS
All patients	**46**
Subsequent treatment, N (%)	**3**
Chemo(immuno)therapy	**1**
Bendamustine/Rituximab	
Chlorambucil/Obinutuzumab	1
BCL2 (Venetoclax)	**2**
Rituximab/Venetoclax	1
Venetoclax	1

TTNT	Modified FAS
Descriptives	
Events, N (%)	3 (6.5)
Median, months [95% confidence interval]	NR
Survival, % [95% confidence interval]	
month 6	100 [NE]
month 12	100 [NE]
month 18	95.3 [89.0, 100.0]
month 24	93.0 [85.3, 100.0]
month 30	93.0 [85.3, 100.0]
month 36	93.0 [85.3, 100.0]



8. Secondary endpoint – Feasibility

Feasibility parameters (until EOS)	**SP**
All patients	**52**
Number of cycles with dose ≥ 1 of study treatment	**52**
Mean	25.85
Standard deviation	14.15
Median	30
IQR	13 – 38
Range	1 – 42

Feasibility parameters (until EOS)	**SP**	
All patients	**52**	
Ongoing treatment until regular EOS?	**52**	
Yes	29	(55.8)
No	23	(44.2)
Reason for treatment discontinuation	**23**	
Adverse event (AE)	11	
Death	2	
AE and death	3	
Refuse to cooperate	4	
AE and refuse to cooperate	2	
AE and withdrawal of consent	1	
AE and other, namely due to the hospice stay[4]	1	

Feasibility parameters	**SP**	
All patients	**52**	
Patient received ≥ 1 dose modification, until EOT, N (%)	**52**	
No	7	(13.5)
Yes	45	(86.5)
Dose modifications due to adverse event (AE), N (%)	**52**	
No	15	(28.8)
Yes	37	(71.2)

[4] The termination was decided jointly by the patient and doctor.

E. ADVERSE EVENTS

1. Adverse events information

Timeframe for reporting adverse events: AEs until 28 days after end of treatment; SAEs and AEs of special interest until end of study; AEs of particular interest until end of study or start of next treatment for CLL
Assessment type: non-systematic
Dictionary used: MedDRA, current version (v24.0 – v28.0)

2. Adverse event reporting group

Safety endpoints were reported for the safety population.

3. Adverse event preferred terms

- **Blood and lymphatic system disorders**

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Blood and lymphatic system disorders	**CTC**	**28**	**(4.0)**
Anaemia	2 3	3 6	(0.4) (0.9)
Haemorrhagic diathesis	2	1	(0.1)
Hyperchromic anaemia	2	1	(0.1)
Leukocytosis	3	2	(0.3)
Neutropenia	3 4	3 4	(0.4) (0.6)
Normochromic normocytic anaemia	3	1	(0.1)
Thrombocytopenia	1 2 3	3 3 1	(0.4) (0.4) (0.1)

Cardiac disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Cardiac disorders	**CTC**	**37**	**(5.3)**
Acute cardiac event	5	1	(0.1)
Angina pectoris	1	3	(0.4)
Aortic valve incompetence	1	1	(0.1)
Aortic valve stenosis	1	1	(0.1)
Atrial fibrillation	2	2	(0.3)
	3	3	(0.4)
Bradycardia	2	2	(0.3)
Cardiac failure	2	2	(0.3)
	3	5	(0.7)
Cardiac valve disease	3	1	(0.1)
Cardiorenal syndrome	3	1	(0.1)
Chronic coronary syndrome	2	1	(0.1)
Chronotropic incompetence	2	1	(0.1)
Heart failure with preserved ejection fraction	2	1	(0.1)
Hypertensive heart disease	3	1	(0.1)
Mitral valve incompetence	1	2	(0.3)
Myocardial infarction	5	1	(0.1)
Palpitations	1	5	(0.7)
	2	1	(0.1)
Tachycardia	1	1	(0.1)
Tricuspid valve incompetence	1	1	(0.1)

Ear and labyrinth disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Ear and labyrinth disorders	**CTC**	**16**	**(2.3)**
Deafness	1	2	(0.3)
Ear discomfort	1	1	(0.1)
Ear haemorrhage	1	1	(0.1)
Ear pain	1	2	(0.3)
Vertigo	1	5	(0.7)
	2	5	(0.7)

Endocrine disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Endocrine disorders	**CTC**	**1**	**(0.1)**
Goitre	2	1	(0.1)

Eye disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Eye disorders	**CTC**	**18**	**(2.6)**
Cataract	1	1	(0.1)
	2	4	(0.6)
Conjunctival haemorrhage	1	1	(0.1)
Dry eye	2	1	(0.1)
Ectropion	2	1	(0.1)
Eye haematoma	1	1	(0.1)
Eye haemorrhage	1	2	(0.3)
Eyelid haematoma	1	2	(0.3)
Ocular discomfort	2	1	(0.1)
Ocular hyperaemia	2	1	(0.1)
Pterygium	3	1	(0.1)
Visual acuity reduced	2	1	(0.1)
Visual impairment	2	1	(0.1)

Gastrointestinal disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Gastrointestinal disorders	**CTC**	**74**	**(10.6)**
Abdominal pain	1	1	(0.1)
Abdominal pain upper	1	3	(0.4)
	2	2	(0.3)
Aphthous ulcer	1	2	(0.3)
Ascites	1	1	(0.1)
Change of bowel habit	1	1	(0.1)
Chronic gastritis	2	1	(0.1)
Constipation	1	5	(0.7)
	2	5	(0.7)
Diarrhoea	1	13	(1.9)
	2	5	(0.7)
	3	2	(0.3)
Dry mouth	1	2	(0.3)
Flatulence	2	2	(0.3)
Gastritis erosive	2	1	(0.1)
Gastrointestinal disorder	3	1	(0.1)
Gingival bleeding	1	1	(0.1)
	2	1	(0.1)
Inguinal hernia	1	1	(0.1)
	3	1	(0.1)
Melaena	1	1	(0.1)
Mouth haemorrhage	1	1	(0.1)
Nausea	1	7	(1.0)
	2	3	(0.4)
Stomatitis	1	1	(0.1)
	2	1	(0.1)
Tongue coated	1	1	(0.1)
Tooth disorder	2	1	(0.1)
Vomiting	1	5	(0.7)
	2	2	(0.3)

General disorders and administration site conditions

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
General disorders and administration site conditions	**CTC**	**47**	**(6.7)**
Asthenia	1	1	(0.1)
	2	1	(0.1)
Chest pain	1	1	(0.1)
	2	1	(0.1)
Face oedema	1	1	(0.1)
Fatigue	1	10	(1.4)
	2	2	(0.3)
Gait disturbance	1	1	(0.1)
General physical health deterioration	1	1	(0.1)
	2	1	(0.1)
	3	1	(0.1)
Influenza like illness	2	1	(0.1)
Localised oedema	2	1	(0.1)
Oedema	1	1	(0.1)
Oedema peripheral	1	11	(1.6)
	2	5	(0.7)
Peripheral swelling	2	1	(0.1)
Pyrexia	1	1	(0.1)
	2	3	(0.4)
Sensitivity to weather change	1	1	(0.1)
Swelling	1	1	(0.1)

Hepatobiliary disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Hepatobiliary disorders	**CTC**	**4**	**(0.6)**
Biliary colic	2	1	(0.1)
Cholecystitis	3	1	(0.1)
Gallbladder mucocoele	3	1	(0.1)
Gallbladder rupture	3	1	(0.1)

Immune system disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Immune system disorders	**CTC**	**2**	**(0.3)**
Drug hypersensitivity	1	1	(0.1)
	3	1	(0.1)

Infections and infestations

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Infections and infestations	**CTC**	**111**	**(15.9)**
Abscess	3	1	(0.1)
Body tinea	2	1	(0.1)
Breast abscess	2	1	(0.1)
Bronchitis	1	1	(0.1)
	2	5	(0.7)
	3	1	(0.1)
Campylobacter gastroenteritis	3	1	(0.1)
Conjunctivitis	2	1	(0.1)
COVID-19	1	7	(1.0)
	2	14	(2.0)
	3	3	(0.4)
	5	1	(0.1)
COVID-19 pneumonia	3	2	(0.3)
	5	1	(0.1)
Cystitis	2	1	(0.1)
Eye infection	2	1	(0.1)
Fungal skin infection	1	1	(0.1)
Gastroenteritis	2	1	(0.1)
Herpes simplex	3	1	(0.1)
Herpes zoster	1	1	(0.1)
	2	1	(0.1)
	3	1	(0.1)
Infected bite	1	1	(0.1)
Infected skin ulcer	2	1	(0.1)
Infection	1	1	(0.1)
	2	1	(0.1)
Influenza	1	1	(0.1)
	2	3	(0.4)
Laryngitis	2	2	(0.3)
Localised infection	1	1	(0.1)
	2	2	(0.3)
Lymph gland infection	2	1	(0.1)
Nasopharyngitis	1	6	(0.9)
	2	7	(1.0)
Oral candidiasis	1	1	(0.1)
Otitis media	2	1	(0.1)
Pneumonia	1	1	(0.1)
	2	3	(0.4)
	3	5	(0.7)
	5	2	(0.3)
Pneumonia pneumococcal	3	1	(0.1)
Pneumonia respiratory syncytial viral	2	1	(0.1)

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Infections and infestations *(cont.)*	**CTC**	**111**	**(15.9)**
Respiratory tract infection	2	5	(0.7)
Septic shock	4	1	(0.1)
Sinusitis	2	2	(0.3)
Skin infection	2	1	(0.1)
Tracheitis	1	1	(0.1)
Upper respiratory tract infection	2	1	(0.1)
Urinary tract infection	1	1	(0.1)
	2	8	(1.1)
	3	1	(0.1)

Injury, poisoning and procedural complications

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Injury, poisoning and procedural complications	**CTC**	**34**	**(4.9)**
Ankle fracture	2	1	(0.1)
Bone contusion	1	1	(0.1)
Concussion	2	1	(0.1)
Contusion	1	8	(1.1)
	2	2	(0.3)
Fall	1	3	(0.4)
	2	1	(0.1)
	3	2	(0.3)
Head injury	1	1	(0.1)
Immunisation reaction	1	1	(0.1)
	2	1	(0.1)
Ligament rupture	1	1	(0.1)
Ligament sprain	1	1	(0.1)
Limb injury	1	1	(0.1)
	2	2	(0.3)
Muscle rupture	1	1	(0.1)
Post procedural haemorrhage	2	1	(0.1)
Rib fracture	1	1	(0.1)
Road traffic accident	2	1	(0.1)
Tendon rupture	1	1	(0.1)
Thoracic vertebral fracture	1	1	(0.1)
Wound	2	1	(0.1)

Investigations

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Investigations	**CTC**	**32**	**(4.6)**
Biopsy skin	1	1	(0.1)
Blood creatinine decreased	1	1	(0.1)
Blood creatinine increased	1	8	(1.1)
	2	2	(0.3)
Blood urea increased	2	1	(0.1)
C-reactive protein increased	2	2	(0.3)
Candida test positive	1	1	(0.1)
Cardiac murmur	1	1	(0.1)
Electrocardiogram ST-T segment abnormal	2	1	(0.1)
Gamma-glutamyltransferase increased	2	1	(0.1)
Hepatic enzyme increased	2	2	(0.3)
	3	1	(0.1)
Immunoglobulins decreased	1	1	(0.1)
Lymphocyte count increased	3	1	(0.1)
Neutrophil count decreased	3	1	(0.1)
Urological examination	2	2	(0.3)
Weight decreased	1	4	(0.6)
	2	1	(0.1)

Metabolism and nutrition disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Metabolism and nutrition disorders	**CTC**	**35**	**(5.0)**
Decreased appetite	1	2	(0.3)
Dehydration	1	3	(0.4)
	2	3	(0.4)
	3	1	(0.1)
Folate deficiency	1	1	(0.1)
	2	2	(0.3)
Hypercalcaemia	2	1	(0.1)
	4	1	(0.1)
Hyperkalaemia	1	2	(0.3)
	2	2	(0.3)
	3	1	(0.1)
Hyperuricaemia	1	2	(0.3)
	2	1	(0.1)
Hypoglycaemia	1	1	(0.1)
	2	1	(0.1)
Hypokalaemia	1	3	(0.4)
	2	1	(0.1)
	3	2	(0.3)
Hyponatraemia	2	1	(0.1)
Iron deficiency	2	1	(0.1)
Vitamin D deficiency	2	3	(0.4)

Musculoskeletal and connective tissue disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Musculoskeletal and connective tissue disorders	**CTC**	**34**	**(4.9)**
Arthralgia	1	1	(0.1)
	2	1	(0.1)
Arthritis	1	1	(0.1)
Back pain	1	3	(0.4)
	2	4	(0.6)
Flank pain	2	1	(0.1)
Foot deformity	2	1	(0.1)
Gout	2	1	(0.1)
Intervertebral disc protrusion	3	1	(0.1)
Limb discomfort	1	1	(0.1)
Muscle spasms	1	4	(0.6)
	2	1	(0.1)
Muscular weakness	1	1	(0.1)
	2	3	(0.4)
Musculoskeletal pain	1	3	(0.4)
Myalgia	1	1	(0.1)
	2	1	(0.1)
Osteochondrosis	3	1	(0.1)
Pain in extremity	1	2	(0.3)
	2	1	(0.1)
Tenosynovitis	2	1	(0.1)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**CTC**	**16**	**(2.3)**
Basal cell carcinoma	1	1	(0.1)
	2	6	(0.9)
	3	1	(0.1)
Bowen's disease	1	1	(0.1)
	2	1	(0.1)
Lipoma	1	2	(0.3)
Malignant fibrous histiocytoma	2	1	(0.1)
Seborrhoeic keratosis	2	1	(0.1)
Squamous cell carcinoma of skin	2	2	(0.3)

Nervous system disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Nervous system disorders	**CTC**	**43**	**(6.2)**
Ataxia	1	1	(0.1)
Burning sensation	3	1	(0.1)
Cerebral infarction	2	1	(0.1)
Cerebrovascular accident	3	2	(0.3)
Cervicobrachial syndrome	3	1	(0.1)
Dementia	2	1	(0.1)
	3	1	(0.1)
Dementia with Lewy bodies	5	1	(0.1)
Demyelinating polyneuropathy	1	1	(0.1)
Dizziness	1	2	(0.3)
Dysgeusia	1	1	(0.1)
Guillain-Barre syndrome	3	1	(0.1)
Headache	1	7	(1.0)
	2	5	(0.7)
Hypotonia	2	1	(0.1)
Memory impairment	2	1	(0.1)
Meningism	2	1	(0.1)
Orthostatic intolerance	1	1	(0.1)
Paraesthesia	1	1	(0.1)
Parkinson's disease	2	1	(0.1)
Polyneuropathy	1	1	(0.1)
Post herpetic neuralgia	2	1	(0.1)
Restless legs syndrome	2	1	(0.1)
Sciatica	2	1	(0.1)
Seizure	2	1	(0.1)
Syncope	1	3	(0.4)
	2	2	(0.3)
	3	1	(0.1)

Psychiatric disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Psychiatric disorders	**CTC**	**8**	**(1.1)**
Anxiety	1	1	(0.1)
Delirium	3	1	(0.1)
Depression	2	1	(0.1)
Hallucination	3	1	(0.1)
Insomnia	2	1	(0.1)
Listless	1	1	(0.1)
Sleep disorder	1	1	(0.1)
Substance-induced mood disorder	1	1	(0.1)

Renal and urinary disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Renal and urinary disorders	**CTC**	**13**	**(1.9)**
Acute kidney injury	2	1	(0.1)
	3	2	(0.3)
Bladder irritation	2	1	(0.1)
Dysuria	1	1	(0.1)
	2	1	(0.1)
Nephrolithiasis	1	1	(0.1)
Nocturia	1	1	(0.1)
Pollakiuria	1	1	(0.1)
Renal failure	1	1	(0.1)
	2	1	(0.1)
Urinary incontinence	1	1	(0.1)
Urinary retention	2	1	(0.1)

Reproductive system and breast disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Reproductive system and breast disorders	**CTC**	**5**	**(0.7)**
Benign prostatic hyperplasia	1	1	(0.1)
	2	1	(0.1)
Gynaecomastia	2	1	(0.1)
Hydrocele	3	1	(0.1)
Prostatitis	2	1	(0.1)

Respiratory, thoracic and mediastinal disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Respiratory, thoracic and mediastinal disorders	**CTC**	**46**	**(6.6)**
Chronic obstructive pulmonary disease	4	1	(0.1)
Cough	1	2	(0.3)
	2	3	(0.4)
Dyspnoea	1	5	(0.7)
	2	3	(0.4)
Dyspnoea exertional	1	5	(0.7)
	2	3	(0.4)
Epistaxis	1	11	(1.6)
	2	6	(0.9)
Nasal congestion	1	1	(0.1)
Oropharyngeal pain	1	2	(0.3)
Pharyngeal haemorrhage	1	1	(0.1)
Pleural effusion	2	1	(0.1)
Pulmonary hypertension	1	1	(0.1)
Rhinorrhoea	1	1	(0.1)

Skin and subcutaneous tissue disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Skin and subcutaneous tissue disorders	**CTC**	**35**	**(5.0)**
Actinic keratosis	2	3	(0.4)
Alopecia	1	1	(0.1)
Dermatitis	1	2	(0.3)
Dry skin	1	2	(0.3)
Eczema	1	2	(0.3)
Erythema	1	1	(0.1)
Nail bed inflammation	1	1	(0.1)
Night sweats	1	2	(0.3)
Petechiae	1	3	(0.4)
Pruritus	2	1	(0.1)
Rash	1	4	(0.6)
	2	3	(0.4)
	3	2	(0.3)
Rosacea	2	1	(0.1)
Seborrhoeic dermatitis	2	2	(0.3)
Skin haemorrhage	2	1	(0.1)
Skin lesion	1	1	(0.1)
	2	2	(0.3)
Superficial inflammatory dermatosis	2	1	(0.1)

Surgical and medical procedures

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Surgical and medical procedures	**CTC**	**6**	**(0.9)**
Blepharoplasty	2	1	(0.1)
Cataract operation	2	2	(0.3)
Dental implant removal	1	1	(0.1)
Dental implantation	2	2	(0.3)

Vascular disorders

PTs of AEs by MedDRA SOC and CTC grade		SP	
All documented adverse events (AE), N (%)		**697**	
Vascular disorders	**CTC**	**52**	**(7.5)**
Extravasation blood	1	1	(0.1)
Haematoma	1	27	(3.9)
	2	7	(1.0)
Haemorrhage	2	1	(0.1)
Hypertension	1	1	(0.1)
	2	2	(0.3)
Hypertensive crisis	2	1	(0.1)
Hypotension	1	4	(0.6)
	2	3	(0.4)
Pallor	1	1	(0.1)
Peripheral venous disease	1	1	(0.1)
	2	1	(0.1)
Phlebitis	2	1	(0.1)
Post thrombotic syndrome	1	1	(0.1)

4. Serious adverse event

Adverse Events with deadly outcome

AEs with CTC grade = 5		SP
All documented AEs with CTC grade = 5, N		**7**
Cardiac disorders	**CTC**	
Acute cardiac event	5	1
Myocardial infarction	5	1
Infections and infestations	**CTC**	
COVID-19	5	1
COVID-19 pneumonia	5	1
Pneumonia	5	2
Nervous system disorders	**CTC**	
Dementia with Lewy bodies	5	1

Serious AE

Safety population: case level	SP	
All documented adverse events (AE)	**697**	
Marked as serious AE (SAE), N (%)	**697**	
No	634	(91.0)
Yes	63	(9.0)

Patient-level analysis of serious adverse events (AEs)

All cases	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	33	(63.5)
Max. CTC grades 3 – 5	28	(53.8)
Max. CTC grades 1 – 2	5	(9.6)
Max. CTC grade 3	20	(38.5)
Max. CTC grade 4	1	(1.9)
Max. CTC grade 5	7	(13.5)

Serious AEs are listed per SOC category, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system, for the occurrence of at least 1 AE, and per PT for the occurrence of at least 5 AEs.

Blood and lymphatic system disorders

Blood and lymphatic system disorders	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	1	(1.9)

Blood and lymphatic system disorders Anaemia	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	1	(1.9)

Blood and lymphatic system disorders Neutropenia	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Blood and lymphatic system disorders Thrombocytopenia	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Cardiac disorders

Cardiac disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	8 (15.4)

Cardiac disorders Atrial fibrillation	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Cardiac disorders Cardiac failure	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	4 (7.7)

Cardiac disorders Palpitations	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Ear and labyrinth disorders

Ear and labyrinth disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Ear and labyrinth disorders Vertigo	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Endocrine disorders

Endocrine disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Eye disorders

Eye disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Eye disorders Cataract	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Gastrointestinal disorders

Gastrointestinal disorders	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	3	(5.8)

Gastrointestinal disorders Abdominal pain upper	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Gastrointestinal disorders Constipation	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Gastrointestinal disorders Diarrhoea	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Gastrointestinal disorders Nausea	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Gastrointestinal disorders Vomiting	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

General disorders and administration site conditions

General disorders and administration site conditions	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	1	(1.9)

General disorders and administration site conditions Fatigue	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

General disorders and administration site conditions Oedema peripheral	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Hepatobiliary disorders

Hepatobiliary disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	2 (3.8)

Immune system disorders

Immune system disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Infections and infestations

Infections and infestations	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	13 (25.0)

Infections and infestations Bronchitis	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Infections and infestations COVID-19	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	2 (3.8)

Infections and infestations Nasopharyngitis	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Infections and infestations Pneumonia	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	5 (9.6)

Infections and infestations Respiratory tract infection	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Infections and infestations Urinary tract infection	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Injury, poisoning and procedural complications

Injury, poisoning and procedural complications	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	5 (9.6)

Injury, poisoning and procedural complications Contusion	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Injury, poisoning and procedural complications Fall	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	2 (3.8)

Investigations

Investigations	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Investigations Blood creatinine increased	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Investigations Weight decreased	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Metabolism and nutrition disorders

Metabolism and nutrition disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Metabolism and nutrition disorders Dehydration	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Metabolism and nutrition disorders Hyperkalaemia	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Metabolism and nutrition disorders Hypokalaemia	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Musculoskeletal and connective tissue disorders

Musculoskeletal and connective tissue disorders	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	1	(1.9)

Musculoskeletal and connective tissue disorders Back pain	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Musculoskeletal and connective tissue disorders Muscle spasms	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	3	(5.8)

Nervous system disorders

Nervous system disorders	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Nervous system disorders Headache	Serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Nervous system disorders Syncope	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Psychiatric disorders

Psychiatric disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Renal and urinary disorders

Renal and urinary disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	2 (3.8)

Reproductive system and breast disorders

Reproductive system and breast disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Respiratory, thoracic and mediastinal disorders

Respiratory, thoracic and mediastinal disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	2 (3.8)

Respiratory, thoracic and mediastinal disorders Cough	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Respiratory, thoracic and mediastinal disorders Dyspnoea	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Respiratory, thoracic and mediastinal disorders Dyspnoea exertional	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Respiratory, thoracic and mediastinal disorders Epistaxis	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Skin and subcutaneous tissue disorders

Skin and subcutaneous tissue disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Skin and subcutaneous tissue disorders Rash	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Surgical and medical procedures

Surgical and medical procedures	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Vascular disorders

Vascular disorders	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Vascular disorders Haematoma	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

Vascular disorders Hypotension	Serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	0 (0.0)

5. Non-serious adverse event

Patient-level analysis of non-serious adverse events (AEs)

All cases	Non-serious AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	52 (100)
Max. CTC grades 3 – 5	24 (46.2)
Max. CTC grades 1 – 2	28 (53.8)
Max. CTC grade 3	21 (40.4)
Max. CTC grade 4	3 (5.8)
Max. CTC grade 5	0 (0.0)

Non-serious AEs are listed per SOC category, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system, for the occurrence of at least 1 AE, and per PT for the occurrence of at least 5 AEs.

Blood and lymphatic system disorders

Blood and lymphatic system disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	17	(32.7)

Blood and lymphatic system disorders Anaemia	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Blood and lymphatic system disorders Neutropenia	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Blood and lymphatic system disorders Thrombocytopenia	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Cardiac disorders

Cardiac disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	12	(23.1)

Cardiac disorders Atrial fibrillation	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	3	(5.8)

Cardiac disorders Cardiac failure	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Cardiac disorders Palpitations	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Ear and labyrinth disorders

Ear and labyrinth disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	11	(21.2)

Ear and labyrinth disorders Vertigo	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Endocrine disorders

Endocrine disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	0	(0.0)

Eye disorders

Eye disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	10	(19.2)

Eye disorders Cataract	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Gastrointestinal disorders

Gastrointestinal disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	29	(55.8)

Gastrointestinal disorders Abdominal pain upper	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Gastrointestinal disorders Constipation	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	10	(19.2)

Gastrointestinal disorders Diarrhoea	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	12	(23.1)

Gastrointestinal disorders Nausea	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Gastrointestinal disorders Vomiting	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

General disorders and administration site conditions

General disorders and administration site conditions	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	27	(51.9)

General disorders and administration site conditions Fatigue	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	12	(23.1)

General disorders and administration site conditions Oedema peripheral	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	11	(21.2)

Hepatobiliary disorders

Hepatobiliary disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	2	(3.8)

Immune system disorders

Immune system disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	2	(3.8)

Infections and infestations

Infections and infestations	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	39	(75.0)

Infections and infestations Bronchitis	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Infections and infestations COVID-19	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	19	(36.5)

Infections and infestations Nasopharyngitis	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Infections and infestations Pneumonia	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Infections and infestations Respiratory tract infection	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	3	(5.8)

Infections and infestations Urinary tract infection	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Injury, poisoning and procedural complications

Injury, poisoning and procedural complications	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	18	(34.6)

Injury, poisoning and procedural complications Contusion	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Injury, poisoning and procedural complications Fall	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	2	(3.8)

Investigations

Investigations	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	21	(40.4)

Investigations Blood creatinine increased	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Investigations Weight decreased	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Metabolism and nutrition disorders

Metabolism and nutrition disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Metabolism and nutrition disorders Dehydration	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Metabolism and nutrition disorders Hyperkalaemia	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Metabolism and nutrition disorders Hypokalaemia	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Musculoskeletal and connective tissue disorders

Musculoskeletal and connective tissue disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Musculoskeletal and connective tissue disorders Back pain	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Musculoskeletal and connective tissue disorders Muscle spasms	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Nervous system disorders

Nervous system disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	24	(46.2)

Nervous system disorders Headache	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	9	(17.3)

Nervous system disorders Syncope	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Psychiatric disorders

Psychiatric disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Renal and urinary disorders

Renal and urinary disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	11	(21.2)

Reproductive system and breast disorders

Reproductive system and breast disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Respiratory, thoracic and mediastinal disorders

Respiratory, thoracic and mediastinal disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	19	(36.5)

Respiratory, thoracic and mediastinal disorders Cough	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Respiratory, thoracic and mediastinal disorders Dyspnoea	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Respiratory, thoracic and mediastinal disorders Dyspnoea exertional	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Respiratory, thoracic and mediastinal disorders Epistaxis	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

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Skin and subcutaneous tissue disorders

Skin and subcutaneous tissue disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	21	(40.4)

Skin and subcutaneous tissue disorders Rash	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Surgical and medical procedures

Surgical and medical procedures	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Vascular disorders

Vascular disorders	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	29	(55.8)

Vascular disorders Haematoma	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Vascular disorders Hypotension	Non-serious AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

6. All adverse event

Patient-level analysis of all adverse events (serious + non-serious AEs)

All cases	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	52	(100)
Max. CTC grades 3 – 5	37	(71.2)
Max. CTC grades 1 – 2	15	(28.8)
Max. CTC grade 3	27	(51.9)
Max. CTC grade 4	3	(5.8)
Max. CTC grade 5	7	(13.5)

AEs are listed per SOC category, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system, for the occurrence of at least 1 AE, and per PT for the occurrence of at least 5 AEs.

Blood and lymphatic system disorders

Blood and lymphatic system disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	17	(32.7)

Blood and lymphatic system disorders Anaemia	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	9	(17.3)

Blood and lymphatic system disorders Neutropenia	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Blood and lymphatic system disorders Thrombocytopenia	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Cardiac disorders

Cardiac disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	18	(34.6)

Cardiac disorders Atrial fibrillation	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Cardiac disorders Cardiac failure	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	4 (7.7)

Cardiac disorders Palpitations	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	5 (9.6)

Ear and labyrinth disorders

Ear and labyrinth disorders	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	11 (21.2)

Ear and labyrinth disorders Vertigo	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	6 (11.5)

Endocrine disorders

Endocrine disorders	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	1 (1.9)

Eye disorders

Eye disorders	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	11 (21.2)

Eye disorders Cataract	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	5 (9.6)

Gastrointestinal disorders

Gastrointestinal disorders	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	30 (57.7)

Gastrointestinal disorders Abdominal pain upper	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	4 (7.7)

Gastrointestinal disorders Constipation	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	10 (19.2)

Gastrointestinal disorders Diarrhoea	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	12 (23.1)

Gastrointestinal disorders Nausea	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	6 (11.5)

Gastrointestinal disorders Vomiting	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	4 (7.7)

General disorders and administration site conditions

General disorders and administration site conditions	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	28 (53.8)

General disorders and administration site conditions Fatigue	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	12 (23.1)

General disorders and administration site conditions Oedema peripheral	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	11 (21.2)

Hepatobiliary disorders

Hepatobiliary disorders	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	3 (5.8)

Immune system disorders

Immune system disorders	All AEs
All patients (SP)	**52**
Max. CTC grade, N (%)	
Max. CTC grades 1 – 5	2 (3.8)

Infections and infestations

Infections and infestations	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	43	(82.7)

Infections and infestations Bronchitis	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Infections and infestations COVID-19	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Infections and infestations Nasopharyngitis	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Infections and infestations Pneumonia	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Infections and infestations Respiratory tract infection	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	3	(5.8)

Infections and infestations Urinary tract infection	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Injury, poisoning and procedural complications

Injury, poisoning and procedural complications	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	21	(40.4)

Injury, poisoning and procedural complications Contusion	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Injury, poisoning and procedural complications Fall	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Investigations

Investigations	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	21	(40.4)

Investigations Blood creatinine increased	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Investigations Weight decreased	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Metabolism and nutrition disorders

Metabolism and nutrition disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Metabolism and nutrition disorders Dehydration	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Metabolism and nutrition disorders Hyperkalaemia	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Metabolism and nutrition disorders Hypokalaemia	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Musculoskeletal and connective tissue disorders

Musculoskeletal and connective tissue disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Musculoskeletal and connective tissue disorders Back pain	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	7	(13.5)

Musculoskeletal and connective tissue disorders Muscle spasms	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	11	(21.2)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Nervous system disorders

Nervous system disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	26	(50.0)

Nervous system disorders Headache	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	9	(17.3)

Nervous system disorders Syncope	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Psychiatric disorders

Psychiatric disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Renal and urinary disorders

Renal and urinary disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	12	(23.1)

Reproductive system and breast disorders

Reproductive system and breast disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Respiratory, thoracic and mediastinal disorders

Respiratory, thoracic and mediastinal disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	19	(36.5)

Respiratory, thoracic and mediastinal disorders Cough	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	5	(9.6)

Respiratory, thoracic and mediastinal disorders Dyspnoea	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Respiratory, thoracic and mediastinal disorders Dyspnoea exertional	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Respiratory, thoracic and mediastinal disorders Epistaxis	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

Skin and subcutaneous tissue disorders

Skin and subcutaneous tissue disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	21	(40.4)

Skin and subcutaneous tissue disorders Rash	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	8	(15.4)

Surgical and medical procedures

Surgical and medical procedures	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	4	(7.7)

Vascular disorders

Vascular disorders	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	29	(55.8)

Vascular disorders Haematoma	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	20	(38.5)

Vascular disorders Hypotension	All AEs	
All patients (SP)	**52**	
Max. CTC grade, N (%)		
Max. CTC grades 1 – 5	6	(11.5)

F. ADDITIONAL INFORMATION

1. Global Substantial Modifications

	DE	**AT**
First Submission, protocol v1.1		
EC submission	02.12.2020	15.07.2021
EC Approval	26.03.2021	24.11.2021
CA submission	02.12.2020 The initial application was rejected by the CA (BfArM).	15.07.2021
CA submission 2nd round	15.03.2021	
CA approval	23.04.2021	17.09.2021
Amendment 1, protocol v.2.0	**No substantial changes**	
EC submission	21.07.2022	21.07.2022
EC Approval	08.08.2022	25.08.2022
CA submission	21.07.2022	21.07.2022
CA approval	03.08.2022	30.07.2022
Send to DE & AT sites	09.09.2022	15.09.2022
Amendment 2, protocol v.3.0	**Substantial changes:** – New formulation of study drug: In addition to capsules also film tablets will be provided – Updated information according to current SmPC for acalabrutinib: hypertension has been added.	
EC submission	25.10.2023	25.10.2023
EC Approval	13.11.2023	17.11.2023
CA submission	25.10.2023	25.10.2023
CA approval	14.11.2023	14.11.2023
Send to DE & AT sites	19.12.2023	19.12.2023
CTR-Transition, protocol v3.0		
CTIS submission	29.02.2024	
CTIS approval	29.04.2024	
Send to DE & AT sites	16.07.2024	
Amendment 3/SM-2, protocol v3.0		
CTIS submission	10.01.2025	
CTIS approval	26.02.2025	10.03.2025
Send to DE & AT sites	11.03.2025	

2. Global interruptions and re-starts

None to report

3. Limitations, addressing sources of potential bias and imprecisions and Caveats

None to report

4. A declaration by the submitting party on the accuracy of the submitted information

The sponsor certifies that the information provided in this report is accurate to their best of their knowledge and that they have performed due diligence in its collection and reporting.

- Date of this report: 30.12.2025